14. (**Thrice Amended**) ~~A vector including a DNA construct~~ The composition of claim 22, wherein each of said constructs is provided in a vector including ~~and~~ a selectable marker permitting transfection of the ~~DNA~~ construct into host cells and selection of transfectants containing the construct.

18. (**Twice Amended**) A mammalian cell which contains and expresses the nucleic acid composition ~~at least one nucleic acid construct~~ of claim 22, 23, or 49.

22. (**Twice Amended**) A nucleic acid composition comprising at least two genetic constructs, each encoding a chimeric protein,

(a) a first construct encoding a first chimeric protein comprising at least one ligand-binding domain and a transcriptional activation domain which is heterologous thereto,

(b) a second construct encoding a second chimeric protein comprising at least one ligand-binding domain which may be the same or different from a ligand binding domain of the first chimeric protein, and a DNA binding domain which is heterologous thereto,

wherein the first and second of said chimeric proteins together (i) bind to a ligand to form a ligand cross-linked protein complex, and (ii) in a ligand dependent manner, activate transcription of a gene having a transcriptional regulatory element to which the DNA binding domain binds.

23. (**Twice Amended**) A nucleic acid composition comprising at least two genetic constructs, each encoding a chimeric protein,

(a) a first construct encoding a first chimeric protein comprising at least one ligand-binding domain and a signal initiation domain which is heterologous thereto; and,

(b) a second construct encoding a second chimeric protein comprising at least one ligand-binding domain which may be the same or different from ~~a~~ the ligand binding domain of the first chimeric protein, and an intra-cellular localization domain which is heterologous thereto,

wherein the first and second of said chimeric proteins together (i) bind to a ligand to form a ligand cross-linked protein complex, and (ii) in a ligand dependent manner, activate an intra-cellular signaling pathway.

49. (**Amended**) A nucleic acid composition comprising at least two genetic constructs, each encoding a chimeric protein,

(a) a first construct encoding a first chimeric protein comprising at least one ligand-binding domain, a signal initiation domain which is heterologous thereto, and a cytoplasmic domain of a cell surface receptor; and,

(b) a second construct encoding a second chimeric protein comprising at least one ligand-binding domain which may be the same or different from ~~a~~ the ligand binding domain of the first chimeric protein, a signal initiation domain which is heterologus thereto and which may be the same or different from ~~a~~ the signal initiation domain of the first chimeric protein, and a cytoplasmic domain of a cell surface receptor which may be the same or different from ~~a~~ the cytoplasmic domain of a cell surface receptor of the first chimeric protein,

wherein the first and second of said chimeric proteins together (i) bind to a ligand to form a ligand cross-linked protein complex, and (ii) in a ligand dependent manner, activate a cellular signaling pathway.

55. (**Amended**) The composition of claim 49 in which the ligand-binding domain of at least one of the chimeric proteins is ~~a variant of~~ an FKBP domain, wherein said FKBP domain comprises FKBP12 or a variant thereof, and wherein said variant comprises substitution of one or more of Tyr26, Phe36, Asp37, Tyr82 and Phe99 with another amino acid residue.

57. (**Amended**) The composition of claim 49 in which the ligand binding domain of at least one of the chimeric proteins specifically binds to FK506, FK520, rapamycin, or a derivative of FK506, FK520, or rapamycin ~~either~~.

61. (**Amended**) The composition of claim 22 in which the ligand-binding domain of at least one of the chimeric proteins is ~~a variant of~~ an FKBP domain, wherein said FKBP domain

comprises FKBP12 or a variant thereof, and wherein said variant comprises substitution of one or more of Tyr26, Phe36, Asp37, Tyr82 and Phe99 with another amino acid residue.

63. (**Amended**) The composition of claim 22 in which the ligand binding domain of at least one of the chimeric proteins specifically binds to FK506, FK520, rapamycin, or a derivative of FK506, FK520, or rapamycin ~~either~~.

66. (**Amended**) The composition of claim 23 in which the ligand-binding domain of at least one of the chimeric proteins is ~~a variant of~~ an FKBP domain, wherein said FKBP domain comprises FKBP12 or a variant thereof, and wherein said variant comprises substitution of one or more of Tyr26, Phe36, Asp37, Tyr82 and Phe99 with another amino acid residue.

68. (**Amended**) The composition of claim 23 in which the ligand binding domain of at least one of the chimeric proteins specifically binds to FK506, FK520, rapamycin, or a derivative of FK506, FK520, or rapamycin ~~either~~.

REMARKS

Claims 14, 17, 18, 22-24, 30, 32, 33, and 48-69 are the pending claims in the present application. Claims 14, 18, 22, 23 and 49-69 are currently under consideration. Applicants will cancel non-elected claims upon indication of allowable subject matter. Applicants cancel, without prejudice, claims 56, 62 and 67. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election/Restrictions

Applicants note that claims 17, 24, 30, 32, 33 and 48 are withdrawn from consideration as being drawn to a nonelected invention. Applicants reiterate for the record, however, that the election was made with traverse. To further clarify any confusion regarding this point, Applicants refer the Examiner to the response filed April 3, 2001.

Sequence Compliance

The present application is a continuation of U.S. Application Serial No. 08/388,653, filed February 14, 1995, which has issued as U.S. Pat. No. 5,869,337. Applicants direct the Examiner's attention to the paper copy and attorney verification statement filed August 7, 2002. Applicants' submission is believed to bring the application into compliance with the rules regarding sequences.

Additionally, the Examiner has pointed out that Applicants have made reference to proteins containing a PEST sequence (page 21, line 31), and has requested that Applicants submit a substitute sequence listing to explicitly describe this sequence. Applicants respectfully disagree with the need to reference this sequence in the sequence listing. A PEST sequence is a consensus sequence motif well known in the art and found in a wide variety of proteins. Requiring an applicant to explicitly recite the sequence of such widely understood proteins and consensus sequences would turn biotechnology patent applications into tomes that recite extensive information commonly available in the art. This is not the intention of sequence listings. Applicants are permitted to refer to proteins well known in the art such as PDGF (platlet-derived growth factor) by name alone, without the need to explicitly provide this well known sequence in a sequence listing, because one of skill in the art can readily appreciate the meaning of the term in light of the art and in light of the specification. Absent some modification of the sequence by the applicant or absent a need to provide a unique sequence in order to satisfy the requirements for patentability under 35 U.S.C. 112, first paragraph, Applicants contend that it is not necessary to explicitly recite a well known sequence or sequence motif to comply with the sequence requirements. Accordingly, Applicants contend that the present application satisfies the sequence requirements and reconsideration and withdrawal of this objection is respectfully requested.

Information Disclosure Statement

The information disclosure filed June 26, 2002 is objected to for allegedly failing to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP 609. On March 26, 2003, Applicants submitted the necessary references, and this submission is believed to obviate the objection.

Specification

3. The amendment filed 27 August 2002 is objected to under 35 U.S.C. 132 for allegedly introducing new matter into the disclosure. The Office Action alleges that recitation of the following passage represents new matter: "the contents of each of these applications is hereby incorporated by reference into the present disclosure. The full contents of related cases PCT/US94/01617, PCT/US94/01660 and PCT/US94/08008 are also incorporated by reference into the present disclosure". Applicants traverse this objection to the extent that it is maintained in light of Applicants' amendment to the specification.

Applicants have amended the specification to delete reference to the aforementioned PCT applications. However, Applicants have retained the incorporation by reference language because such language is supported by the disclosure, as filed, and accordingly does not constitute new matter. Support for this subject matter can be found on page 82, lines 16-19.

> "All publications and patent application cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference."

Applicants' amendments and arguments are believed to obviate this objection to the specification.

4. The disclosure is objected to over certain informalities. Applicants' amendments to the specification are believed to obviate the objections.

a. Applicants have amended the description of Figure 15 to define the abbreviations used in the accompanying drawing.

b. Applicants have amended the paragraph containing page 50, line 28 to correctly refer to Fig. 6A.

c. Applicants have amended the paragraph containing page 49, line 29 to define the abbreviation "TAC". Applicants point out that this abbreviation is defined and discussed in detail in the publication (PNAS 88: 8905-8909) cited in that same paragraph.

d. The Examiner has pointed out the alleged presence of handwritten notes on pages 45, 47 and 57. Applicants have amended the particular paragraphs on both page 45 and page 47 to incorporate the handwritten notes. However, Applicants did not find any handwritten notes on page 57, and thus have not made any amendments with respect to this page of the disclosure.

Applicants' amendments are believed to obviate the objection. However, if the Examiner maintains the objection with respect to page 57, Applicants request clarification so that we may adequately address any informalities which may still exist in the specification.

Response to Amendment

5. Applicants note that all rejections of claims 1, 6, 20, 21, 31, 36-39 and 45 have been withdrawn in view of cancellation of these claims.

Applicants note that the rejection of claims 14, 18, 22 and 23 under 35 U.S.C. 112, second paragraph, has been withdrawn.

Applicants note that the rejection of claim 18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-76 of U.S. Patent No. 6,140,120 has been withdrawn.

Applicants note that the rejection of claim 14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-127 of U.S. Patent No. 6,046,047 has been withdrawn.

Applicants note that the rejection of claim 18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-76 of U.S. Patent No. 6,140,120 has been withdrawn.

Applicants note that the provisional rejection of claim 18 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44-54 of copending Application No. 09/582,916 has been withdrawn.

Applicants note that the rejection of claim 18 as not being patentably distinct from claims 4 and 10 of commonly assigned U.S. Patent No. 6,117,680 has been withdrawn.

Applicants note that the rejection of claims 18 and 22 under 35 U.S.C. 102(b) as being anticipated by Spencer et al. has been withdrawn.

Applicants note that the rejections of claims 14, 18, 22 and 23 under 35 U.S.C. 102(b) as being anticipated by Young et al., under 35 U.S.C. 102(b) as being anticipated by Crabtree et al., under 35 U.S.C. 102(b) as being anticipated by Liu et al., and under 35 U.S.C. 102(b) as being anticipated by Rivera et al. have been withdrawn.

Applicants note that the rejection of claim 14 under 35 U.S.C. 102(b) as being unpatentanble over Arvidsson et al. has been withdrawn.

Applicants note that the rejection of claims 22 and 23 under 35 U.S.C. 102(b) as being anticipated by Becker et al. has been withdrawn.

Applicants note that the rejection of claims 14, 18, 22 and 23 under 35 U.S.C. 102(e) as being anticipated by Natesan et al. has been withdrawn.

Applicants note that the rejection of claims 18 and 22 under 35 U.S.C. 103(a) as being unpatentable over Spencer et al. has been withdrawn.

Applicants note that the rejection of claims 14 and 18 under 35 U.S.C. 103(a) as being unpatentable over Spencer et al. of over Arvidsson et al. have been withdrawn.

6. Claim 18 is rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 62-129 of U.S. Patent No. 6,165,787. Claims 23, 50-53 and 65-69 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-71 of U.S. Patent No. 6,043,082. Claims 18, 22 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 87-142 and 154-162 of U.S. Patent No. 5,869,337. Claims 14, 18 and 64 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 72-202 of U.S. Patent No. 5,834,266. Claims 14, 18 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 14-28, 37, 38, 40, 43-52 and 60-62 of U.S. Patent No. 6,117, 680. Applicants will submit terminal disclaimers, if necessary, upon indication of allowable subject matter.

Response to Arguments

Claims 18, 23 and 52 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Arvidsson et al. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

Applicants have amended the claims to more particularly point out the claimed subject matter. The pending claims are explicitly directed to compositions comprising at least two chimeric genetic constructs. In contrast, the prior art provides compositions wherein only one of the two proteins are chimeric proteins. Additionally, Applicants point out that the pending claims are directed to two or more chimeric constructs that encode proteins which together bind

to a ligand to form a complex. This feature of the invention is neither taught nor suggested by the prior art.

Applicants note for the record that the amendments to the claims do not indicate acquiescence to the rejection. Applicants' amendments are made solely to expedite prosecution of commercially relevant embodiments of the invention, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are requested.

New Grounds of Rejection

Claims 55, 56, 61, 62, 66 and 67 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one of skill in the art that applicants had possession of the claimed invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

As stated in the prior Office Action, the standard for assessing compliance with the written description requirement has been outlined in detail by the Guidelines for the Examination of Patent Applications which indicate that possession of the invention can be demonstrated in many ways including "by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention." Thus, there does not appear to be any disagreement between Applicants and the Examiner in terms of the criteria that should be used to evaluate the pending claims with respect to compliance with the requirements under 35 U.S.C. 112, first paragraph.

The standard outlined in the Guidelines is supported by the Federal Circuit's finding in The Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1997 U.S. App. LEXIS 18221, 43 U.S.P.Q.2D (BNA) 1398 (Fed. Cir. 1997). The Federal Circuit addressed the question of how to adequately describe a genus of materials. In outlining that which constitutes an adequate description of a genus with respect to genetic material, the court asserted that adequate description requires more than the gene or protein name.

> "[A] cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation

> of the sequence of nucleotides that make up the DNA. See Fiers, 984 F.2d at 1171, 25 U.S.P.Q.2D (BNA) at 1606. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus **or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."** (emphasis supplied) 119 F.3d at 1566

Accordingly, for the description of a genetic invention to be deemed adequate to describe the genus that the claims encompass requires either a recitation of the structure (i.e., sequence) of a representative number of members of the genus **or** a recitation of the common features of the members of the claimed genus. This "recitation of structural features common to the members of the genus" is analogous to the way in which chemical genera are described, and provides features which readily allow one of skill in the art to recognize the claimed invention. This is in contrast to the way in which the claimed subject matter was recited in Lilly, where nucleic acids were claimed by the name of the cDNA and its origin, without any recitation of sequence or common structural or functional characteristics that could be used by one of skill in the art to readily envision the claimed sequences.

> "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." 119 F.3d at 1566

Applicants submit that the pending claims define the claimed subject matter in terms of generic formulae that indicate with specificity what the generic claims encompass, and accordingly meet the guidelines set forth above and comply with the written description requirement. The pending claims describe the claimed genus with respect to both structural and

functional characteristics, and these structural and functional characteristics readily allow one of skill in the art to envision the claimed subject matter.

In short, the specification details the design and functional attributes of the chimeric constructs to which the pending claims are directed. This description of the claimed subject matter according to both structural and functional characteristics allows one to readily envision the claimed subject matter, and furthermore stands in sharp contrast to the way in which sequences were described in *Lilly*. Accordingly, Applicants submit that based on both the Guidelines for the Examination of Patent Applications, and based on the recent findings of the Federal Circuit, Applicants have satisfied the requirements under 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 14, 18, 22, 23 and 49-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The Office Action points out alleged ambiguities in the language used in the above referenced claims. Applicants contend that the claims are clear and concise, and that one of skill in the art can readily assess their metes and bounds. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to further clarify the language recited in each claim. Applicants' amendments are made solely to expedite prosecution, and are not in acquiescence of the rejection. Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 14 and 18 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Becker et al. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

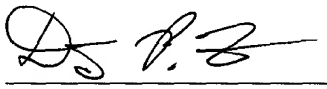
Applicants maintain that the claims are not anticipated by Becker et al. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out the claimed subject matter. Applicants'

amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Amended claims 14 and 18 are now dependent on and further describe claim 22 which is not anticipated by Becker et al. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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